Male Occupational Reproductive Hazards

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Studies assessing reproductive function among male workers were rare in the United States before the discovery of sterility and infertility in 1977 among employees of a pesticide formulating plant in central California. Subsequently, the etiologic agent, dibromochloropropane (DBCP), has been shown in numerous studies of humans and animals to produce similar effects. While studies on the influence of workplace exposures to various chemicals on reproductive function have proliferated during the past five years, no other single agent has approached the dramatic effects exhibited by DBCP. Other agents that have been evaluated and have shown some adverse effects are reviewed critically. Studies of spontaneous abortion or congenital abnormalities in children of wives of men exposed to anesthetic gases and DBCP indicate that pregnancy outcome, as well as infertility and sterility, is an important outcome measure.

Concern about male reproductive hazards resulting from occupational exposures is relatively recent. Historically, research into occupational reproductive problems, either in men or women, has been inadequate, reflecting this lack of interest. Worker protection policies aimed at controlling this problem have been discriminatory, primarily directly aimed against one group—women—and have usually resulted in the exclusion of all women from certain jobs "for their own protection." For this reason, reproductive hazards have been considered primarily a women's issue.

Most studies concerning the effects of chemicals on human spermatogenesis have focused on two areas: (1) the therapeutic use of drugs as possible male contraceptives or as stimulators of sperm production in subfertile men and (2) potential spermatotoxic side effects of drugs administered for therapeutic purposes. However, not until the testicular toxicity of dibromochloropropane (DBCP) was recognized in chemical workers in 1977[1] did it become generally accepted that the male reproductive system can be adversely affected by occupational or environmental exposures to chemicals.

Most external agents known to alter testicular function are pharmacologic agents. These include various hormones (testosterones, progesterones, estrogens and prednisone); alkylating agents (cyclophosphamide, chlorambucil, doxorubicin and methotrexate); nitroamino compounds (nitrofuranes and nitropyrroles); dichloroacetyldamines, and antitestosterone agents (cyproterone acetate).[2] Of the few studies done on workplace exposures, none of the chemical agents investigated either before or after 1977 have had the pronounced effects of DBCP.

Dibromochloropropane

DBCP will be discussed in some detail because of its pronounced effects. A liquid nematocidal agent, it has been used since the mid-1950's. Its primary value was its effectiveness on perennial crops without damaging the plants. Common crops treated with the chemical in the United States included citrus, grapes, peaches, pineapple, soybeans and tomatoes. It was used on bananas in Central America and Israel. Since 1979 its only allowed use in the United States is for pineapples in Hawaii.

Initial Observations

In 1961 DBCP was shown in laboratory animals to be a mild skin and mucous membrane irritant, to cause hepatic and renal damage and to produce testicular

Refer to: Whorton MD: Male occupational reproductive hazards, *In* Occupational disease—New vistas for medicine. West J Med 1982 Dec; 137:521-524.

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atrophy.[3] It was shown to be an animal carcinogen in 1973[4] and an in vivo mutagen in 1975,[5] as well as producing infertility and sterility in human males in 1977.[1]

The discovery of the adverse testicular effects in humans is interesting and shows why one must listen closely to patients. The problem was discovered by the workers of the California pesticide formulation plant, not by physicians or scientists. The number of workers in the agricultural chemicals department where DBCP was processed was small and the workers were young enough to actively want children. The workers noted there was a paucity of children fathered by the men after each had started to work in that department. After considerable discussion, one worker convinced five coworker volunteers to submit semen samples for analyses; all were grossly abnormal (azoospermic or severely oligospermic [fewer than 20 million sperm cells per ml of seminal fluid]). These results were sent to me as a consultant to the local union, although I had not previously seen the men or known about the semen samples. When repeated sperm counts were similar to the original ones, the remainder of the workers who, at the time, worked with agricultural chemicals were examined. Of the 36 men examined (100 percent of the at-risk group), 11 had had vasectomies previously; thus only 25 submitted fresh semen samples. Nine were azoospermic, three were oligospermic and 13 were normospermic.

As a group, there were no other abnormal physical or laboratory findings, except for elevated levels of follicle stimulating hormone and luteinizing hormone for men with low or absent sperm counts. There was a direct correlation between length of employment in that department and abnormally low sperm count.

These initial data from the men in the plant who worked with agricultural chemicals led to a larger study of all of the plant employees. Careful assessment of the data from the first 36 examinations made it clear that there was no need for an exhaustive medical workup on each of the subsequent participants. Accordingly, an abbreviated medical history questionnaire and physical examination strategy were devised. The questionnaire focused on the genitourinary system and emphasized reproductive history.

Studies of Workers

Of the entire 310 men employed by the company, 196 were examined, including the original 36. Semen samples were obtained from 142 of the 196 men examined. Forty-five men had had vasectomies and nine declined to give a semen sample. Thirty-five men providing semen samples "never" had had exposure to DBCP, while 107 "ever" exposed provided semen samples. The median sperm count was 46×10^6 per ml for the group of 107 men ever exposed to DBCP and 79×10^6 per ml for the 35 men never exposed. The Kolmogorov-Smirnov test showed the exposed and nonexposed distributions to be dissimilar ($\alpha = 0.05$). In the larger study, the same was true.

Of the 100 chemicals used in the plant, four had been shown to be toxic to the male reproductive system. Due to the relative quantities of production, the agent considered most suspect in this facility was dibromochloropropane.[6] Based on the reported findings, the two producers of DBCP (Shell Chemical Company and Dow Chemical Company) conducted medical evaluations of their workers and found similar results.[7,8] The association between exposure to DBCP and testicular dysfunction was strengthened when it was found that the only common exposure among the workers at the three plants was DBCP.

Seven separate studies were done in 1977 and 1978 on male workers who had been exposed to DBCP. Not all of these studies have been published nor was the same methodology used in all of them. All, however, showed that occupational exposure to DBCP has disastrous effects on testicular function: 14.5 percent of the subjects were azoospermic and another 21 percent were oligospermic. Finally, not all of the men in all of the studies were currently exposed to DBCP at the time of the studies.[7-12] In addition to these studies, recent studies on factory workers in Mexico[13] and field-workers in Hawaii[14] and Costa Rica (R. Smith, MD, Medical Director, Castle and Cooke, Inc., oral communication, 1981) have shown similar results of testicular dysfunction.

Women

The reproductive effects of DBCP on women are essentially unknown; in the various studies too few women were employed in jobs with exposure to the chemical to make an evaluation possible. However, Kharrazi and co-workers evaluated pregnancy outcomes of married women employed as banana workers in 14 kibbutzim in the Jordan Valley of Israel.[15] The data showed an increase in spontaneous abortion among the wives after their husbands' exposure to DBCP. Before exposure, 6.6 percent of pregnancies resulted in spontaneous abortion compared with a 19.8 percent spontaneous abortion rate in pregnancies after exposure. Whether this represents an effect on the sperm cell or the developing embryo or fetus is unclear.

Biopsy Findings

Histological examinations from testicular biopsies of men exposed to DBCP have shown a selective decrease or loss of spermatogenic cells without any other consistent testicular defect. The presumed mechanism was a direct toxic effect on the primary spermatogonia. In severely affected men, the seminiferous tubules were devoid of spermatogenic cells with only Sertoli's cells remaining.[6,16] In the less severely affected, there was a decrease in the amount of cellularity within the seminiferous tubules. There was no evidence of inflammation. There was minimal evidence of increase in fibrosis and interstitial changes.

Follow-up

Follow-up of the men in three of the earlier studies has been reported. In one study group, all of the azoospermic men remained azoospermic.[17] Both Lanham[9] and Potashnik (Potashnik G, Yanai-Inbar I, Sober I: Recovery of human testicular function sup-

TABLE 1.—*Environmental Agents Causing Adverse Male Reproductive Effects in Humans*

Alcohol
Anesthetic gases
Carbon disulfide
Dibromochloropropane (DBCP)
Diethylstilbestrol (male offspring in utero exposure)
Estrogens (in oral contraceptive manufacturing)
Ethylene dibromide
Chlordecone (Kepone)
Lead
Marijuana
Radiation (ionizing)
Toluene diamine

pression caused by dibromochloropropane, unpublished data, March 1981) report recovery to normospermic ranges for some of the previously azoospermic men. All three follow-up evaluations have reported relatively quick improvement in oligospermic men after exposure ceases.

One study done several years after cessation of DBCP production showed no differences between exposed and nonexposed men. The authors interpreted the data as evidence of recovery from a temporary effect.[18] Two evaluations of pineapple workers six months after cessation of DBCP use showed no difference between exposed men and nonexposed controls.[19,20]

Other Agents

Table 1 shows environmental agents that have been shown to cause adverse male reproductive effects in humans. Some of these agents have shown only marginal effects; others have shown both positive and negative results, most likely representing difference in exposures. Most studies have been on semen.[2] Agents for which other parameters have been examined are discussed below.

While anesthetic gases have been studied for reproductive outcome in numerous studies, the reevaluation of the data from the United States and Great Britain of operating room-based physicians showed paternal exposure to be associated with an increase in birth defects among their offspring.[21] A recent study of semen quality among male anesthesiologists was negative.[22]

In male workers manufacturing oral contraceptives, gynecomastia, decreased libido and impotence have developed.[23] The changes are reversible with removal from exposure.

Studies on three separate chemical agents and a study of a mixture of three chemicals have been published and reported as negative: epichlorohydrin,[24] polybrominated biphenols,[25] para-tertiary butyl benzoic acid[26] and glycerine production products.[27]

Two studies on carbaryl, done primarily on the same population, showed no abnormalities in sperm count.[28,29] The latter study did show a significant decrement in normal sperm morphology. Further study is necessary to understand the morphology findings.

More recent studies on lead, ethylene oxide, glycol ethers, a variety of chemicals at a Bahamanian chemical plant, mercury oxide and other Health Hazard Evaluations by the National Institute of Occupational Safety and Health have been done, but are not yet published.

Another method of evaluating chemical effects on testicular function is to assess pregnancy outcomes in wives of the exposed men. In this situation, one is looking for spontaneous abortions, stillbirths or congenital abnormalities. Two such studies described earlier for anesthetic gases[21] and DBCP[15] were positive for congenital abnormalities and spontaneous abortions, respectively. Carmelli and co-workers (A case-control study of the relationship between exposure to 2,4-D and spontaneous abortions in humans, unpublished SRI International Report, 1981) reported no increase in spontaneous abortions among wives of men exposed to 2,4-D. Several other studies are currently being conducted. The proposed mechanism is a mutagenic effect on the sperm cell DNA, resulting in an adverse pregnancy outcome.

Reproductive studies secondary to workplace exposures of male workers have proliferated rapidly during the past five years. While many methodological problems still exist for these studies (a discussion beyond the scope of this review), one can only predict that many more such studies will be done in the future. While DBCP has clearly caused the most obvious effects, other agents are likely to be present and have yet to be discovered. The future of occupational reproductive studies appears to be unlimited.

A practical approach to help develop priorities in deciding which chemical exposure to study would be the use of animal data. The most important data would be those in which the animals' testicular function is adversely affected at dose levels that have little or no effect on other organ systems. The effects of DBCP in humans could have been predicted using such a measure.

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BOOK REVIEW

RECENT ADVANCES IN OCCUPATIONAL HEALTH—Edited by J. C. McDonald, MD, FRCP, FFCM, FFOM. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1981. 292 pages, $40.00 (softbound).

This book, with its 24 topics discussed by 33 authors in only 292 pages, has something for almost everyone. Its prose is generally engaging and occasionally enlivened by charts, pictures, formulas and tables. Although styles and formats vary, they are not jarring; problems in each topic are often highlighted and conclusions summarized. The topics, which are both usual and unusual, could appeal to a variety of readers. Of greatest interest to clinicians would be the sections about work hazards, such as asbestos and other mineral fibers, microwave, deepsea diving, carcinogenic effects of metals, protection of workers involved in energy production and agriculture in the Third World. The sections on investigative methods and worker protection are both brief and basic and would probably be of greatest interest to professionals in training. Because of the compact coverage of a diversity of subjects (including social aspects), this volume may be of particular use to policymakers. It frequently points up controversies and frailties, especially in the section on investigative methods. Many of the numerous authors are well known in the field; information given is as up-to-date as any can be in a book; most of the articles have 30 or more references, and the index is good. The weaknesses are quite minor and mainly relate to the slight fustiness of the section on investigative methods and the limitation of some of the examples to Great Britain.

Overall, the volume should be of interest to those with an interest in or responsibility for occupational health practice or policies, and those who are casting about for some stimulation, a quick overview or good bibliographies.

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